CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-214

PHARMACOLOGY/TOXICOLOGY REVIEW

NDA 21-214 Rescula®

CIBA Vision

Review and evaluation of Pharmacology and Toxicology Data

Division of Analgesics, Anti-inflammatory, and Ophthalmic Drug Products
HFD-550
Reviewer: Susan D. Wilson, D.V.M., Ph.D.

NDA Number: N21-214

Serial Number: 000
Letter Date: February 14, 2000
Center Stamp Data February 16, 2000
Type of Submission: Original NDA

Information to Sponsor: No (X)

Completion Date: June 26, 2000

Sponsor or Agent:
CIBA Vision Corp.
U.S. Ophthalmics
11460 Johns Creek Parkway
Duluth, GA 30097-1556

Manufacturer (if different) for drug substance:

[redacted]

Manufacturer for drug product:
CIBA Vision Sterile Manufacturing
6515 Kitimat Road
Mississauga, Ontario LS5N 2X5
Canada

Drug name: 1° - Rescula®
2° - unoprostone isopropyl ophthalmic solution
3° - UIOS

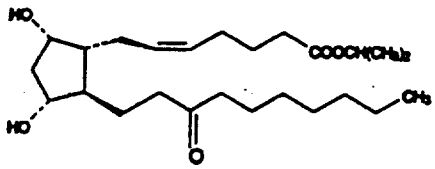
Drug Substance - Unoprostone isopropyl [USAN]
- Isopropyl unoprostone [JAN]
- Unoprostone [INN]

Primary Metabolite - unoprostone free acid
- M1

Chemical Name: Isopropyl (+)-(Z)-7-[(1R, 2R, 3R, 5S)-3,5-dihydroxy-2-(3-oxooctadecyl)-cyclopentyl] hept-5-enoate

CAS Number (if provided by sponsor): 120373-24-2

Structure: $C_{25}H_{44}O_5$



Molecular Weight: 424.62

Relevant IND/NDA/DMF:

Drug Class: Docosanoid analogue of $PGF_{2\alpha}$ metabolite

Indication: Reduction of intraocular pressure in patients with open angle glaucoma and ocular hypertension

Clinical Formulation (and components): The drug product is packaged in polypropylene bottles with a 5-ml fill volume [commercially available].

Unoprostone Isopropyl	1.5
Polysorbate 80, NF	
Benzalkonium chloride, NF	0.15
Edetate disodium, USP	
Mannitol, USP	
Sodium hydroxide NF	
Hydrochloric acid NF	
Water for injection, USP	

Several different formulations were used in the nonclinical studies. These will be described for the individual studies. The nonclinical formulation designated is the same as the clinical formulation.

Route of Administration: Ocular instillation

Proposed Clinical Protocol: Not applicable

Studies Reviewed within this submission:

Report No.	Report Date	Study Title	Test Material Lot
PHARMACOKINETIC STUDIES			
Ocular Biodistribution/Bioavailability Studies			
Rabbit			
001-G/CP-96	July 23, 1996	Comparison of the *in vitro* corneal permeation of MS-016 and Rescula® eye drop formulations [Vol. 1.50, pp. 1-20]	

Report No.	Report Date	Study Title	Test Material Lot
008-I/CP-98	Jan. 1, 1999	*In vitro* corneal permeation of unoprostone isopropyl [UF-021] and its metabolization in the isolated pig eye [Vol. 1.50, pp. 21-41]	Not provided
Not provided	Not provided	Ocular penetration of UF-021, A new prostaglandin-related compound, in the rabbit eye [Vol. 1.50, pp. 42-51]	Not provided
Not provided	Not provided	Distribution of UF-021 in rabbit eye tissue after single topical administration [Vol. 1.50, pp. 52-70]	
016 96	Nov. 4, 1997	Comparison of ocular bioavailability of two UF-021 eyedrop formulations, Rescula® and MS-016, after a single instillation in the pigmented rabbit [Vol. 1.50; pp. 108-236]	
CO6/U/001 98	Oct. 15, 1998	0.15% unoprostone isopropyl ophthalmic solution. Ocular bioavailability after a single instillation into the right conjunctival sac of pigmented rabbits [Vol. 1.50; pp. 237-323]	
007-I/PK-98	Nov. 16, 1998	Comparison of the *in vivo* ocular penetration of unoprostone isopropyl versus unoprostone free acid [Vol. 1.50; pp. 324-333]	
Systemic Pharmacokinetics			
Ocular Administration			
Rabbit			
AE-1543	Aug. 27, 1991	Pharmacokinetics of UF-021[V] administration to rabbits by eyedrops [Vol. 1.50, pp. 71-107]	
Parenteral Administration			
Rats - IV			
Single Dose			
AE-1410 AE-1543	Aug. 27, 1991	UF-021 Pharmacokinetics [I] ; Unit dosage testing in rats [Vol. 1.51, pp. 1-115]	
Repeated Dose			
AE-1410	Aug. 27, 1991	Pharmacokinetics of UF-021 [2]; Repeated administration to rats [Vol. 1.51; pp. 116-160]	
Dogs – IV			
AE-1410 AE-1543	Aug. 27, 1991	Pharmacokinetics of UF-021 [IV]; Repeated administration to dogs [Vol. 1:51; pp. 218-260]	
Rats – SC			
Not provided	Not provided	*In vivo* kinetics of UF-021 with single subcutaneous administrations in rat [Vol. 1:51; pp. 161-182]	
Rabbits – SC			
AE-1543	Aug. 27, 1991	Pharmacokinetics of UF-021 [III]; Single administration to rabbits [Vol. 1.51; pp. 183 217]	
Metabolism			
In Vitro			
008-I/CP-98	Jan. 1, 1999	*In vitro* corneal permeation of unoprostone isopropyl [UF-021] and it metabolization in the isolated pig eye [Vol. 1.50; pp. 21-41]	Not provided
Drug-Interactions			
Not provided	Not provided	Effect of UF-021 on drug metabolism enzymes [Vol. 1.52; pp. 100-116]	Not provided
PHARMACOLOGY STUDIES			
Efficacy Studies – *In Vivo*			
Rabbits			
3-0c-3001	Not provided	Preliminary study of intraocular pressure reduction and dose-dependency of UF-021 studies in rabbits [Vol. 1.8; pp. 1-11]	

Report No.	Report Date	Study Title	Test Material Lot
YG-0c-3019	Not provided	UF-021 intraocular pressure-reducing effects and dosage dependency studies in rabbits [Vol. 1.8; pp. 12-26]	
YG-0c-3005	Not provided	Preliminary investigation of intraocular pressure lowering effects of UF-021 ophthalmic solution by repeated administration in rabbits [Vol. 1.8; pp. 67-81]	
YG-0c-3031	Not provided	Intraocular pressure lowering effects of UF-021 ophthalmic solution by repeated administration in rabbits [Vol. 1.8; pp. 82-90]	
YG-0c-3030	Not provided	Effect of UF-021 ophthalmic solution on a rabbit model of ocular hypertension induced by water loading [Vol. 1.8; pp. 60-66]	
Cats			
YG-0c-9001	Not provided	Preliminary study of intraocular pressure reduction and dose-dependency of UF-021 - Study in cats [Vol. 1.8; pp. 27-38]	
YG-0c-9003	Not provided	UF-021 intraocular pressure-reducing effects and dosage dependence - Studies in cats [Vol. 1.8; pp. 39-47]	
Monkeys			
YG-0c-5002	Not provided	Intraocular pressure-reducing effects of UF-021 Eye Drops Solution – Studies in monkeys [Vol. 1.8; pp. 48-59]	
Mechanism of Action Studies			
Effect on Aqueous Humor Flow Rate/Production			
Not provided	Not provided	Effect of UF-021 on aqueous humor production in rabbits [Vol. 1.8; pp. 91-96]	
3605D1	April 12, 1996	Effect of Rescula® Eye-Drops on aqueous humor flow rate after a single topical administration in ocular normotensive monkeys [Vol. 1.4; pp. 122-151]	
Effect on Aqueous Humor Outflow			
YG-0c-3028	Not provided	Effect of UF-021 on aqueous humor outflow in rabbits [Vol. 1.8; pp. 97-103]	
YG-0c-9002	Not provided	Effect of UF-021 on aqueous humor outflow in cats [Vol. 1.8; pp. 104-111]	
YG-0c-3016	Not provided	Intraocular pressure-reducing mechanism of UF-021; Interaction with pilocarpine in rabbits and cats [Vol. 1.8; pp. 112-121]	
IOP and Prostaglandins			
TEL-98	Nov. 10, 1999	Endogenous prostaglandins release in radio-telemetry implanted rabbits: Rescula vs. latanoprost [Vol. 1.8; pp. 152-167]	
Not provided	June 22, 1999	The effect of indomethacin pretreatment on the performance of 0.12% unoprostone isopropyl [Rescula] and 0.005% latanoprost [Xalatan] in normotensive dogs [Vol. 1.8; pp. 168-177]	
Not provided	July 26, 1999	Affinity profile of unoprostone for prostaglandin receptors [Vol. 1.8; pp. 178-184]	Not provided
Effects Related to Possible Adverse Reactions			
Not provided	Feb. 12, 1999	Assessment in isolated and perfused retinal pig arteries of the vasoactive properties of unoprostone isopropyl and its metabolite M1 in comparison with latanoprost and its metabolite latanoprost acid [Vol. 1.8; pp. 184-195]	Not provided
Not provided	Nov. 23, 1999	Summary of the effect of Rescula/M1 on the effect of endothelin on contractility of isolated bovine trabecular meshwork and ciliary muscle strips [Vol. 1.8; pp. 196-201]	Not provided

Report No.	Report Date	Study Title	Test Material Lot
Not provided	Not provided	Effects of UF-021 ophthalmic solution on blood flow in rabbit ocular tissue [Vol. 1.8; pp. 202-205]	Not provided
YG-Oc-3033	Not provided	Comparison of the effect of UF-021 ophthalmic solution, a sympathomimetic agent, and a parasympathomimetic agent on pupil diameter in rabbits [Vol. 1.8, pp. 206-212]	
YG-Ei-2001,2002, 2003	Not provided	Effect of UF-021 ophthalmic solution on an experimental conjunctivitis model in rats: Histamine-induced conjunctivitis; Allergic conjunctivitis; Carageenan-induced conjunctival edema [Vol. 1.8, pp. 213-222]	
YG-Ei-3001	Not provided	Effect of UF-021 ophthalmic solution on the course of repair of avulsion wounds of the corneal epithelium in rabbits [Vol. 1.8, pp. 223-230]	
3606F01	Sept. 8, 1999	Ocular blood flow of ocular normotensive monkeys: Effects of 1-month topical treatment of 0.15% unoprostone isopropyl versus 0.005% latanoprost [Vol. 1.8, pp. 231-244]	
3606F02/1351-003	April 27, 1998	Ocular blood flow of ocular normotensive monkeys: Effects of 24-month topical treatment of 0.15% unoprostone isopropyl [Vol. 1.8, pp. 245-254]	Not provided
001-ET1/MK/99	Aug. 4, 1999	Blood flow changes after systemic vasoconstrictor administration in cynomolgus monkeys: Effects of unoprostone isopropyl [UIOS] [Vol. 1.8, pp. 255-266]	Not provided
Comparison with Other Drugs Having Similar Therapeutic Effects			
YG-Oc-3034	Not provided	Comparison of effect of UF-021 ophthalmic solution, prostaglandin E_2, and prostaglandin $F_{2\alpha}$ on intraocular pressure and local ocular findings in rabbits [Vol. 1.8, pp. 271-280]	
YG-Oc-3003, 3004	Not provided	Comparison of IOP-reducing action of UF-021 ophthalmic solution and existing glaucoma treatment agents in rabbits [Vol. 1.8, pp. 281-288]	
YG-Oc-3036	Not provided	Comparative study of intraocular pressure lowering effects of UF-021 ophthalmic solution and carbonic anhydrase inhibitor in rabbits [Vol. 1.8, pp. 289-297]	
YG-Oc-3035	Not provided	Effects of UF-021 metabolites, UF-021 related substances, and decomposed products [degraded UF-021] on intraocular pressure in rabbits [Vol. 1.8, p0. 298-303]	
Not provided	Dec. 20, 1998	The effect of 0.12% unoprostone isopropyl [Rescula] on intraocular pressure in normotensive dogs – A comparison with 0.005% latanoprost [Xalatan] [Vol. 1.8, pp. 304-309]	Not provided
Interactions with Other Drugs			
YG-0c-3009	Not provided	Intraocular pressure reducing action by concomitant use of UF-021 ophthalmic solution and current antiglaucoma drugs [Vol. 1.8, pp. 310-321]	Not provided
1873-47331	Feb. 3, 1995	Effect of concurrent administration of Rescula eyedrops and other antiglaucoma agents after repeated topical instillation on albino rabbit corneas [Vol. 1.8, pp. 322-368]	
003-TEL-98	Dec. 10, 1999	IOP lowering effect of 0.15% unoprostone isopropyl and 0.005% latanoprost in combination in ocular normotensive radio-telemetry implanted rabbits [Vol. 1.9, pp. 1-14]	
005-TEL-98	Dec. 10, 1999	IOP lowering effect of 0.15% unoprostone isopropyl and 2% dorzolamide in combination in ocular normotensive radio-telemetry implanted rabbits [Vol. 1.9, pp. 15-29]	

Report No.	Report Date	Study Title	Test Material Lot
008-TEL98	Dec. 10, 1999	IOP lowering effect of 0.15% unoprostone isopropyl and 0.2% brimonidine in combination in ocular normotensive radio-telemetry implanted rabbits [Vol. 1.9, pp. 30-44]	
Studies Comparing Formulations			
3603D0	July 15, 1996	Comparison of the effects of Rescula® eye-drops, UF-021/MS-016 formulations on intraocular pressure and cardiovascular parameters after a single topical administration in ocular normotensive cynomolgus monkeys [Vol. 1.9, pp. 136-157]	
3603D07	Dec. 18, 1996	Comparison of the effects of UF-021/MS-016 eye-drops on intraocular pressure during an OD vs. BID topical administration in ocular normotensive cynomolgus monkeys [Vol. 1.9, pp. 181-197]	
SAFETY PHARMACOLOGY			
General Pharmacology			
Not provided	Not provided	General Pharmacology of UF-021 [Vol. 1.9; pp. 198-222]	
0050	Dec. 5, 1991	General Pharmacology Study of UF-021 [Vol. 1.9; pp. 198-222]	
Not provided	March 5, 1992	General Pharmacology Study of UF-021 [Vol. 1.10; pp. 1-119]	
PT# 1001280	July 20, 1999	pharmacology data report on compound Cba-1 for CIBA Vision [Vol. 1.10; pp.135-165]	Not provided
TOXICOLOGY STUDIES			
Ocular Toxicity/Irritation Studies			
Rabbits			
Irritation Studies			
3403D02	Dec. 18, 1996	UF-021/MS-019 Eye-drops dose-ranging effects on intraocular pressure after a single topical administration in ocular normotensive New Zealand Rabbits [Vol. 1.9, pp. 45-69]	
YG-Su-3002	Not provided	Test of 14 days continuous topical UF-021 application using rabbits [Vol. 1.13: pp. 1-25]	
0436L42.001	Sept. 23, 1997	30-Day ocular irritation study in rabbits [Vol. 1.13; pp. 26-171]	
YG-Cr-3001	June 7, 1991	Eye mucous membrane irritation tests in repeated instillation of UF-021 for albino rabbits [Vol. 1.13; pp. 172-382]	
Toxicity Studies			
0470LC42.001	Oct. 28, 1997	90-day ocular toxicity study in rabbits [Vol. 1.14 – 1.16]	
0470LC42.002	Feb. 24, 1998	90-day ocular toxicity study in Dutch Belted rabbits [Vol. 1.17-1.19]	

Report No.	Report Date	Study Title	Test Material Lot
0472LC42.001	Nov. 10, 1999	1 year ocular toxicity study of 0.15% unoprostone isopropyl ophthalmic solution [UIOS] in Dutch Belted rabbits [Vol. 1.20-1.23]	
YG-Ac-3002	Dec. 17, 1991	Comparative eye mucous irritation test with Rescula ophthalmic solutions, it analogues, metabolites and degradation products ophthalmic solutions in albino rabbits [Vol. 1.41; pp. 95-157]	
Dogs			
YG-Cr-4001	Jan. 28, 1992	Chronic toxicity study of repeated topical administration of UF-021 to the eyes of beagles [Vol. 1.23-1.24]	
Nonhuman Primates			
3603D08	Feb. 14, 1997	UF-021/MS-019 Dose ranging effects on intraocular pressure during a single topical administration in ocular normotensive cynomolgus monkeys [Vol. 1.9, pp. 70-102]	
1351-003	Oct. 6, 1999	104-week ocular chronic toxicity study in the cynomolgus monkey [Vol. 1.25 (pp. 60-244) – Vol. 1.26]	
1351-007 [Report No. 1502-1351-007]	April 7. 2000	18-month ocular study on iris color changes in the cynomolgus monkey: Unoprostone isopropyl ophthalmic solution versus latanoprost	
Systemic Toxicity Studies			
Acute Studies			
Mice			
4177	Apr. 6, 1988	Acute toxicity tests of UF-021 administered to mice orally and subcutaneously [Vol. 1.11; pp. 1-33]	
YG-PA-1001	Not provided	Preliminary toxicity tests of single intravenous administrations of UF-021 using mice [Vol. 1.11; pp. 34-47]	
YG-Ac-1001	Jan. 10, 1992	Comparative toxicity test of single intravenous administration with Rescula, its related compounds, metabolites, and decomposed products in mouse [Vol. 1.11; 48-108]	
Rats			
4180	Jan. 22, 1992	Toxicity test of UF-025 single intravenous administration in rats [Vol. 1.11; pp. 185-285	
4048	Jan. 17, 1989	Acute toxicity study of UF-021 administered intravenously in rats [Vol. 1.11; 109-184]	
4150	Jan. 22, 1992	Toxicity test of single subcutaneous administration of UF-021 in rats [Vol. 1.12; pp. 1-82]	
Dog			
A49-005	June 11, 1990	Acute toxicity study of UF-021 administered intravenously in beagles [Vol. 1.12; pp. 83-178]	
Repeat Dose Studies			
Mice			
453463 [Report No. 14684]	Apr. 26, 1999	MS-016; 4 week dose confirmation study in mice with administration by gavage [Vol. 1.27; pp. 43-208]	
Rats			
5137	June 1, 1988	Preliminary subacute toxicity tests with 14 days of oral UF-021 administration to rats [Vol. 1.27; pp. 1-42]	
453458 [Report No. 14587]	Oct. 7, 1999	MS-016 [DR 40002 Rescula]: 4week dose confirmation study in rats with administration by gavage [Vol. 1.28]	

Report No.	Report Date	Study Title	Test Material Lot
5519	April 6, 1992	Toxicity test of UF-021 after repeated subcutaneous administration for 12 months and withdrawal of the drug administration for 3 months in rats [Vol. 1.32-33]	
5079	Nov. 14, 1990	Toxicity test in rats through subcutaneous administration of UF-021 for 3 months, followed by successive withdrawal thereof for 1 month [Vol. 1.29]	
Dogs			
B32-001	Jan. 8, 1992	Toxicity study of repeated subcutaneous administration of UF-021 for 3 months in beagles. [Vol. 1.31]	
B34-002	Feb. 5, 1992	Subacute toxicity study of intravenous administration of UF-021 for 13 weeks in beagles [Vol. 1.30]	
D34-0001	Jan. 17, 1992	Toxicity study of repeated-dose subcutaneous administration of UF-021 for 1 year in beagle dogs followed by 1 month recovery study [Vol. 1.34]	
REPRODUCTIVE TOXICOLOGY			
Rats			
E11-0008	July 17, 1990	Effects of subcutaneous UF-021 administration prior to and in the early stages of pregnancy in rats [Vol. 1.42; pp. 1 – 246]	
2067	Mar. 31, 1998	Preliminary tests of oral UF-021 administration during fetal organogenesis in rats [Vol. 1.42; pp. 247-318]	
E12-0007	Feb. 29, 1996	Reproductive and developmental toxicity study of UF-021 dosed subcutaneously in rats during the period of fetal organogenesis [Vol. 1.43-1.44]	
E13-008	Dec. 11, 1991	Effects of subcutaneous UF-021 administration during perinatal and lactation periods in rats [Vol. 1.46-1.47]	
Rabbits			
E18-0006	Dec. 11, 1991	Effects of subcutaneous UF-021 administration during fetal organogenesis in rabbits [Vol. 1.45]	
GENOTOXICITY			
9010	Sept. 10, 1990	Reverse mutation test of UF-021 on bacteria [Vol. 1.48; pp. 16-85]	
9160	Dec. 18, 1991	UF-025 reverse mutagenicity test using bacteria [Vol. 1.48; pp. 86-157]	
760277	Sept. 23, 1997	Unoprostone isopropylate; Mouse lymphoma mutation assay [Vol. 1.48; pp. 158-225]	
9730	Dec. 18, 1991	Chromosomal aberration tests of UF-021 using cultured mammalian cells [Vol. 1.48; pp. 226-317]	
9800	Mar. 12, 1992	Chromosomal aberration tests with mammalian cells in culture of UF-025 [Vol. 1.49; pp. 1-81]	
9430	Sept. 10, 1990	Micronucleus test of UF-021 on mice [Vol. 1.49; pp. 82-137]	
CARCINOGENICITY			
Report No. 17499	Oct. 22, 1999	Unoprostone isopropyl:104 week carcinogenicity study in rats with administration by gavage [Vols. 1.35-1.40]	
SPECIAL TOXICOLOGY			
Rabbit			
8029	Dec. 26, 1989	Tests of UF-021 antigenicity [Vol. 1.41; pp. 1-94]	

Studies not reviewed within this submission:

Report No.	Report Date	Study Title
PHARMACOLOGY		
Not provided*	Not provided	Quantitative *in vivo* study in adult rats of the effects of selective ligature of the ophthalmic vessels on retinal ganglion cell death: Effects of CV-R/001 [Vol. 1.8, pp. 267-271]
Studies conducted with reformulated products		
3603D06**	Oct. 3, 1996	Comparison of the effects of two 0.06% UF-021 eye-drop formulations on intraocular pressure and cardiovascular parameters after a single topical administration in ocular normotensive cynomolgus monkeys [Vol. 1.9, pp. 158-180]
3603D04#	July 15, 1996	Comparison of the effects of Rescula® eye-drops, UF-021/MS-016 and UF-021 cremophor based formulations on intraocular pressure and cardiovascular parameters after a single topical administration in ocular normotensive cynomolgus monkeys [Vol. 1.9, pp. 103-135]
Pharmacokinetics		
Not provided	No provided	Pharmacokinetics of UF-021 eyedrops [Vol. 1.52; pp. 2-28] – This study was a clinical PK study and will be reviewed by the Biopharm Reviewer, Veneeta Tandon.
Not provided	Not provided	Synthesis and stability of UF-021 Compound [Vol. 1.52; pp. 70-99] – This will be reviewed by the Chemistry Reviewer, Allan Fenslau
Genotoxicity		
YG-Mu-6001##	Dec. 20, 1987	Reverse mutation tests of UF-021 using bacteria [Vol. 1.48; pp. 1-15]
Ocular Toxicity###		
YG-Ac-3001###	Dec. 17, 1991	Eye mucous membrane irritation test of frequent topical UF-021 administration for short periods in rabbits [Vol. 1.41; pp. 158-198]
YG-Ac-5001###	Oct. 27, 1987	Eye mucosa irritation tests with single applications of UF-021 ophthalmic solutions using monkey [Vol. 1.41 pp. 199-211]

*This study was not reviewed because it was an ocular pharmacology study in which the test article was administered by the ip route.

**These studies were not reviewed because the formulations used were not relevant.

***This study was conducted with a concentration of UF-021 of 0.06% instead of 0.15% [clinical formulation] and, therefore, does not provide any additional information from the other studies reviewed

#Data presented for Rescula® and UF-021/M-016 are the same as that presented in Study No. 3603D05.

##This study was not reviewed since only 2 strains were evaluated with a maximum drug substance concentration of only 1 gm/plate in the absence of any toxicity.

###These studies do not provide any additional information to that obtained from the repeat dose studies.

LITERATURE NOT REVIEWED
PHARMACOLOGY
Hiroshi, O., et. al. [1995] General pharmacological action of Rescula® [isopropyl unoprostone], a metabolic prostaglandin –class therapeutic agent for glaucoma/ocular hypertension: A comparison with timolol and prostaglandin derivatives. *The Clinical Report* 29[7]:21-34 [Vol. 1.10, pp. 120-133] – **Data in this manuscript, with the exception of that for latanoprost, were the same as that in the studies reviewed below.**

Disclaimer (Use of sponsor's material): Material provided by the Sponsor was used in the preparation of this review.

Introduction/Drug History: - Prostaglandins [PG] exhibit pleiototropic physiological effects. The effects can vary depending on the specific prostaglandin, the organ system or tissue, and/or the species being evaluated. In general, $PGF_{2\alpha}$ induces vasoconstriction [species and vascular bed dependent], bronchial and tracheal smooth muscle contraction [intense bronchospasm in asthmatics], uterine contraction, GI smooth muscle contraction, and H_2O and electrolyte movement into the intestinal lumen. PGs mediate their effects through a number of distinct receptors. $PGF_{2\alpha}$ exerts its effects primarily through the EP_1 and FP receptors. The second messenger for both receptors is phospholipase C.[1]

With respect to ocular effects, PGs are produced by the irides and exhibit both physiologic and pathologic functions. In excess, PGs have been associated with the inflammatory response and play a role in the development of miosis, hyperemia, vascular permeability alterations, and intraocular pressure [IOP] changes. With inflammation there is generally an initial increase in IOP followed by a significant decrease. These various effects are PG, species, and dose dependent.[2] It has been demonstrated that low doses of $PGF_{2\alpha}$ will lower IOP apparently by increasing outflow through the uveoscleral pathway [e.g. "posteriorly through the ciliary body"][3].

Latanoprost, an $F_{2\alpha}$ analogue that is a selective FP receptor agonist, has been approved by the FDA as an ophthalmic solution for the treatment of open angle glaucoma and ocular hypertension in patients that have not tolerated or not responded to other IOP lowering drugs. Administration of latanoprost has been associated with [1] an increase in iris pigmentation in both animals in humans; [2] an increase in palpebral fissures in cynomolgus monkeys; [3] periorbital pigment changes in humans; and [4] an increase in pigment and growth of eyelashes. The changes in humans may be irreversible.

Rescula® Eye Drops was approved in Japan in 1994. It has subsequently been approved in a number of Eastern European, Asian, and South and Central American countries. The approved product differs in final formulation compared to the product under review in both concentration of the drug substance and in the excipients. The concentration of unoprostone isopropyl in the approved product is 0.12% compared to 0.15% in the product under review. The excipients in the approved product are polysorbate 80 and benzalkonium chloride. In addition to these excipients, the product formulation under review includes edetate disodium and mannitol. The major adverse events reported for the approved product [as of Aug. 1998] include irritation [4.52%], corneal erosion [2.66%], keratitis [2.4%], corneal punctate opacity [0.17%], and conjunctival hyperemia [2.29%]. Eyelid pigmentation [<0.1%] and increased number and length of eyelashes [0.12%] have also been reported.

Previous clinical experience: See Medical Review

---

[1] Campbell, W.B. Lipid-Derived Autocoids: Eicosanoids and Platelet-Activating Factor In *The Pharmacological Basis of Therapeutics 8th Edition.* (A.G. Goodman, T.W. Rall, A.S. Nies, and P. Taylor, eds.) McGraw-Hill, Inc. New York, 1993, pp. 600-611.

[2] Collins, B. K and Moore, C.P. Diseases and Surgery of the Canine Anterior Uvea In *Veterinary Ophthalmology 3rd Edition* [K.N. Gelatt, ed.] Lippincott Williams & Wilkins, Philadelphia, 1998, pp. 761-762

[3] Gelatt, K.N. and Brooks, D.E. The Canine Glaucomas In *Veterinary Ophthalmology 3rd Edition* [K.N. Gelatt, ed.] Lippincott Williams & Wilkins, Philadelphia, 1998, p. 737.

INDEX OF STUDIES

Note: A number of different ophthalmic formulations were used. Where appropriate, they are referred to as [redacted] The composition of the various formulations is provided in Appendix 1. The clinical formulation is designated as [redacted]

I. Pharmacology:

A. Efficacy Studies – The following studies were conducted to evaluate intraocular pressure [IOP] reduction in several animal models following administration of UF-021. None of these studies utilized the clinical formulation. The formulations are indicated for each study.

a. **In Vivo Studies** – Rabbit, cat, and monkey

i. **Title: Preliminary study of intraocular pressure reduction and dose-dependency of UF-021 studies in rabbits [Vol. 1.8; pp. 1-11]**
Study Identification: [redacted]
Site: [redacted]
Study Dates: September 16-17, 1987
Formulation and Lot No.: [redacted]
Certificate Analysis: No [X]
Final Report: No date provided
GLP and QA Statements Signed: No [X]
Objective: To evaluate the effects of UF-021 on intraocular pressure in rabbits following ocular instillation.

ii. **Title: UF-021 intraocular pressure-reducing effects and dosage dependency studies in rabbits [Vol. 1.8; pp. 12-26]**
Study Identification: [redacted]
Site: [redacted]
Study Dates: July 24-August 10, 1989
Formulation and Lot No.: [redacted]
Certificate Analysis: No [X]
Final Report: No date provided
GLP and QA Statements Signed: No [X]
Objective: To evaluate the effects of UF-021 on intraocular pressure in rabbits following ocular instillation.

iii. **Title: Preliminary study of intraocular pressure reduction and dose-dependency of UF-021 - Study in cats [Vol. 1.8; pp. 27-38]**
Study Identification: [redacted]
Site: [redacted]
Study Dates: September 18 – October 20, 1987
Formulation and Lot No.: [redacted]
Certificate Analysis: No [X]
Final Report: No date provided
GLP and QA Statements Signed: No [X]

Objective: To evaluate the effects of UF-021 on intraocular pressure in cats following ocular instillation.

iv. Title: **UF-021 intraocular pressure-reducing effects and dosage dependence - Studies in cats [Vol. 1.8; pp. 39-47]**
Study Identification:
Site:
Study Dates: February 15 – March 5, 1991
Formulation and Lot No.:
Certificate Analysis: No [X]
Final Report: No date provided
GLP and QA Statements Signed: No [X]
Objective: To evaluate the effects of UF-021 on intraocular pressure in cats following ocular instillation.

v. Title: **Intraocular pressure-reducing effects of UF-021 Eye Drops Solution – Studies in monkeys[Vol. 1.8; pp. 48-59]**
Study Identification:
Site:
Study Dates: June 22-29, 1990
Formulation and Lot No.:
Certificate Analysis: No [X]
Final Report: No date provided
GLP and QA Statements Signed: No [X]
Objective: To evaluate the effects of UF-021 on intraocular pressure in monkeys following ocular instillation.

vi. Title: **Effect of UF-021 ophthalmic solution on a rabbit model of ocular hypertension induced by water loading [Vol. 1.8; pp. 60-66]**
Study Identification:
Site:
Study Dates: March 26-27, 1991
Formulation and Lot No.:
Certificate Analysis: No [X]
Final Report: No date provided
GLP and QA Statements Signed: No [X]
Objective: To evaluate the effects of UF-021 on intraocular pressure compared to 0.5% timolol and 0.1% prazosin in hypertensive rabbits following ocular instillation.

vii. Title: **Preliminary investigation of intraocular pressure lowering effects of UF-021 ophthalmic solution by repeated administration in rabbits [Vol. 1.8; pp. 67-81]**
Study Identification:
Site:
Study Dates: September 30 – October 29, 1987

Formulation and Lot No.:

Certificate Analysis: No [X]
Final Report: No date provided
GLP and QA Statements Signed: No [X]
Objective: To evaluate the effects of UF-021 on intraocular pressure in rabbits following ocular instillation for 30 consecutive days.

viii. **Title:** **Intraocular pressure lowering effects of UF-021 ophthalmic solution by repeated administration in rabbits [Vol. 1.8; pp. 82-90]**
Study Identification:
Site:
Study Dates: May 7 – July 12, 1991
Formulation and Lot No.:

Certificate Analysis: No [X]
Final Report: No date provided
GLP and QA Statements Signed: No [X]
Objective: To evaluate the effects of UF-021 on intraocular pressure in rabbits following ocular instillation for 50 consecutive days.

Study Design [definitive studies]
Single Dose Studies
- Species/strain/N - male Japanese albino rabbits - N = 6-9/group
  - male and female cats - N = 3-4/ group
  - male Asian macaques - N=3/group
- Dose - 1drop [35 µl]
- Test Articles - Placebo, Range of UF-021 in rabbits
  - Placebo, UF-021 in cats
  - 0.12% UF-021, 0.5% timolol in monkeys [contralateral eye [physiological saline] as well as baseline values served as control] - cross-over design with a 1 week washout period
- Endpoint - IOP [applanation pneumatonograph findings] and Draize scoring at 0.5, 1, 2, 3, 4, 5, and 6 hours following drug administration in all species plus 8 hours in cats and 24 hours in rabbits; Pupil diameter at 0.5, 1, 2, 3, 4, 5, 6, and 24 hours following drug administration in cats in the preliminary study

Repeat Dose Studies
- Species/strain/N - male Japanese albino rabbits - N = 6/group
- Dose - 1drop [35 µl] X 50 days BID
- Concentrations - physiological saline
  - 0.12% UF-021
  - 0.5% timolol [Group 3 rabbits were administered timolol on Days 1-36 and 0.12% UF-021 on Days 37-50]
- Endpoint - IOP [applanation pneumatonograph] - Data presented for 0.5, 1, 2, 3, 4, 5, and 6 hours following drug administration on Days 1, 7, and 40 and at 3 hours following dosing on Days 1, 4, 7, 10, 14, 21, 28, 37, 40, 43, and 50.

Hypertensive Model

- Species/strain/N - male Japanese albino rabbits - N = 5-6/group [10-12 eyes evaluated]
- Dose - 1drop [35 µl]
- Test Article - physiological saline
  - 0.12% UF-021
  - 0.5% timolol
  - 0.1% prazosin
  - all animals were administered 60 mg/kg tap water po immediately prior to drug application
- Endpoint - IOP [applanation pneumatonograph] at 0.5, 1, 2, 3 and 4, hours following drug administration

Results [Individual animal data not provided] - The rank order of sensitivity to the IOP reducing effects was cats > rabbits > monkeys. The decreases in IOP were dose and time-dependent. The maximum changes in IOP are outlined in the table below.

Concentrations - UF-021	Mean ΔIOP_{max}* [mmHg ± S.E.]		
	Rabbit	Cat	Monkey**
0.05-0.06%	-3.9 [-3.7 ± 0.8]		
0.1 –0.12%	-4.9 [4.4 ± 0.4]	-5.7 [-9.0]	1.1 [-2.0]
0.2-0.24%	-5.2 [-5.2 ± 1.2]	-7.2 [-9.7]	

*Values represent maximum change in IOP compared to placebo control animals or baseline [in brackets] in the rabbit and cat and compared to the contralateral or baseline [in brackets] IOP for the monkey.
**Maximum Δ in IOP in contralateral eye [e.g. control eye] was –1 mmHg.

Maximum IOP reduction was observed at 3 hours at 0.12% and 0.24% UF-021 in the rabbit and cat and 1-3 hours in the monkey. Reduction in IOP persisted for 5-6 hours and generally for up to 8 hours compared to pre-instillation values in the rabbits and cat. Statistically significant reduction [minimal magnitude] in IOP in the monkey persisted for up to 4 hours.

Slight congestion of the iris and conjunctiva, which persisted for up to 4 hours, was observed in the rabbit at ≥0.12% UF-021. One of 4 cats at 0.24% UF-021 demonstrated mild conjunctival hyperemia at 6 and 8 hours. No irritation was observed in monkeys. [**Note:** Ocular irritation was observed in 3/5 monkeys in Study 3603D05in which Rescula [0.12% UF-021] was instilled into the eye.]

There was a statistically significant decrease in pupil size in cats at ≥ 0.05% UF-021 with a maximum decrease of approximately 75% at 2-3 hours.

Following water loading in rabbits, all drugs significantly reduced the increase in IOP compared to the saline group IOP: ΔIOP compared to baseline values of +3.9 ± 0.7, +5.3 ± 0.9, and +6.7 ± 0.8 mmHg vs. +11.3 ± 1.7 mmHg for UF-021, timolol, and prazosin vs. saline control.

Tolerance did not develop to UF-021 in rabbits following 50 consecutive days of treatment BID as it did with timolol. There was no cross-tolerance of UF-021 with timolol.

Treatment Day	Mean ΔIOP_{max}* [mmHg]	
	0.12% UF-021	0.5% Timolol
Day 1	-6.6 [-7.8]	-4.0 [-3.7]
Day 7	-5.8 [-8.5]	-1.6 [-3.4]
Day 40	-6.7 [-5.5]	-6.6 [-5.0]**

*Values represent maximum change in IOP compared to placebo control animals or baseline [in brackets]
**These animals were treated with timolol through Day 36 and switched to UF-021 on Day 37

[Note: Table 5: Effect on Pupil Diameter [p. 38] is mislabeled. The header of the table reads "Intraocular Pressure [Mean Value ± S.E. mm Hg]. The Sponsor has been asked to clarify this discrepancy.]

B. Mechanism of Action Studies

a. Effect on Aqueous Humor Production/Flow Rate

i. Title: Effect of UF-021 on aqueous humor production in rabbits [Vol. 1.8; pp. 91-96]
Study Identification: Not provided
Site:
Study Dates: Not provided
Formulation and Lot No.:
Certificate Analysis: No [X]
Final Report: No date provided
GLP and QA Statements Signed: No [X]
Objective: To evaluate the effects of UF-021 on aqueous humor flow rate in rabbits.

Study Design – A single drop [35 µl] of either UF-021 [0.06%] or timolol [0.5%] was instilled into one eye of male Japanese albino rabbits. Either UF-021 VH or physiological saline was administered to the contralateral eye. [N=8 for test article groups; N=24 for control; **Note:** It is not clear what the N of 24 represents for control values – e.g. contralateral eyes and/or separate control animals]. Aqueous humor flow was determined by fluorophotometry 1 hour after test article administration and 12-18 hours following instillation of fluorescein into the eye. IOP was measured [applanation pneumatonograph] before administration and 2 hours after test article instillation.

ii. Title: Effect of Rescula® eye-drops on aqueous humor flow rate after a single topical administration in ocular normotensive monkeys [Vol 1.8; pp. 122-151]
Study Identification:
Site:
Study Dates: Not provided
Formulation and Lot No: Rescula®
Certificate Analysis: No [X]
Final Report: April 12, 1996
GLP and QA Statements Signed: No [X]

Objective: "To evaluate the effects of Rescula® on aqueous humor flow rate in ocular normotensive monkeys using fluorophotometry".

Study Design – This was a two-way crossover study with a washout period of 7-8 days. Male cynomolgus monkeys [N=6; 4-6.5 kg; Shamrock] were anesthetized and administered 10 instillations of 10% fluorescein within 50 minutes. The following day, anesthetized monkeys were administered a single drop [50 µl] of either saline or Rescula® into one eye. IOP and cardiovascular parameters [SAP, DAP, MAP, and HR] were measured prior to and 3 hours following instillation. Fluorophotometry was conducted q30 min. X 3 hours following instillation.

Results – Aqueous humor production, as assessed by aqueous humor flow rate, was not decreased in rabbits administered 0.06% UF-021 [4.28 ± 0.87 µl/min] compared to control values [3.68 ± 0.77 µl/min]. [Note: The assumption is made that a comparable effect on aqueous humor production will be observed at higher concentrations.] Aqueous flow rate was decreased in the timolol group [1.18 ± 0.62 µl/min.]. Findings were similar in the monkey with comparable flow rates in the test article group [0.94 ± 0.17 µl/min.] and the saline treated animals [0.82 ± 0.15 µl/min.]. The magnitude of ΔIOP at 3 hours post instillation was greater in this monkey study [-6.3 ± 1.4 and –4.7 mm Hg compared to baseline and saline controls, respectively] than in the efficacy studies. In addition, ΔIOP was observed in the contralateral untreated eye [-4.5 ± 2.4 mm Hg compared to baseline values].

b. Effect on Aqueous Humor Outflow

i. Title: Effect of UF-021 on aqueous humor outflow in rabbits [Vol. 1.8; pp. 97-104]
Study Identification:
Site:
Study Dates: November 21, 1990 – January 7, 1991
Formulation and Lot No.:
Certificate Analysis: No [X]
Final Report: No date provided
GLP and QA Statements Signed: No [X]
Objective: To evaluate the effects of UF-021 on aqueous humor outflow in rabbits.

Study Design - A single drop [35 µl] of either UF-021 [0.12%] or physiological saline was instilled into one eye of male Japanese albino rabbits [N=4-5; 2 control and test article groups]. Aqueous humor outflow rate was determined by tonography 1 and 2 hours following test article instillation [1 measurement/group].

ii. Title: Effect of UF-021 on aqueous humor outflow in cats [Vol. 1.8; pp. 104-111]
Study Identification:
Site:
Study Dates: January 11 – April 12, 1991
Formulation and Lot No.:
Certificate Analysis: No [X]
Final Report: No date provided
GLP and QA Statements Signed: No [X]

Objective: To evaluate the effects of UF-021 on aqueous humor outflow in cats.

Study Design - A single drop [35 µl] of either UF-021 [0.12%], timolol [0.5%], pilocarpine [4%], or physiological saline was instilled into both eyes of male and female cats [N=5-8]. Aqueous humor outflow rate was determined by tonography 30 minutes, 1 and 4 hours following test article instillation. Measurement in the timolol and pilocarpine groups was made at 30 minutes only. Measurements were performed only once after instillation in 1 eye/animal only.

iii. **Title:** Intraocular pressure-reducing mechanism of UF-021; Interaction with pilocarpine in rabbits and cats [Vol. 1.8; pp. 112-122]

Study Identification:

Site:

Study Dates: June 5, 1989 – October 1, 1990

Formulation and Lot No.:

Certificate Analysis: No [X]

Final Report: No date provided

GLP and QA Statements Signed: No [X]

Objective: To evaluate the effect of UF-021 on aqueous humor outflow in rabbits and cats following co-administration with pilocarpine.

Study Design

	Tests in rabbits			Tests in cats
	Experiment 1	Experiment 2	Experiment 3	
No. of animals and test groups	4 rabbits/group	9 rabbits/group	6 rabbits/group, 2 groups (1 group treated with both UF-021 and pilocarpine and 1 group treated with UF-021 alone)	3 cats/group
UF-021	0.06% eye drops solution 35 µl (21 µg)	0.06% eye drops solution 35 µl (21 µg)	0.06% eye drops solution 35 µl (21 µg)	0.06% eye drops solution 35 µl (21 µg)
Pilocarpine	Pilocarpine eye drops solution* 4% 50 µl (2.0 mg)	Pilocarpine eye drops solution* 4% 35 µl (1.4 mg)	Pilocarpine hydrochloride* 1.5 mg/50 µl physiological saline solution	Pilocarpine eye drops solution* 4% 35 µl (1.4 mg)
Method of administering test sample	Pilocarpine instilled in 1 eye 1 30 minutes UF-021 instilled in both eyes	Pilocarpine instilled in 1 eye 1 5 minutes UF-021 instilled in both eyes	UF-021 instilled in 1 eye 1 1 hour Pilocarpine instilled in both eyes, or no treatment	Pilocarpine instilled in 1 eye 1 5 minutes UF-021 instilled in both eyes

Endpoint – IOP

Results – Aqueous humor outflow was increased in both rabbits and cats with UF-021 alone. The aqueous humor outflow in rabbits was increased by approximately 70% and 45% at 1 and 2 hours following drug instillation, respectively, compared to concurrent control animals. The outflow in the treated eye was 24 and 19 µl/min/mmHg at 1 and 2 hours, respectively, compared to control values of 14 and 13 µl/min/mmHg at 1 and 2 hours, respectively. A decrease in IOP, however, was not observed until 2 hours after drug instillation. The Sponsor also stated that in preliminary experiments [data not shown] there was no increase in outflow at ≥6 hours after UF-021 treatment. The aqueous humor outflow in cats was increased by approximately 100% at 30 and 60 minutes compared to concurrent saline control animals. The outflow in the treated eye was

0.45 and 0.51 µl/min/mmHg at 1 and 2 hours, respectively, compared to control values of 0.25 and 0.27 µl/min/mmHg at 1 and 2 hours, respectively. Outflow rates had returned to baseline by 4 hours following drug instillation although a decrease in IOP was observed for at least 4 hours after drug instillation. Outflow was unaltered by administration of either pilocarpine or timolol in the cat. Pre and post- UF-021 treatment with pilocarpine did not appear to modulate the effect of UF-021 on IOP. Since miotics are associated with a decrease in uveoscleral outflow, [4] the Sponsor states that this suggests that UF-021 does not mediate its effects by an increase in outflow through the uveoscleral pathway. The Sponsor did not include a positive control in this study. Therefore, it is not known whether this system was sensitive enough to detect changes in uveoscleral outflow in these species in which uveoscleral outflow accounts for approximately 3% and 15% of total outflow in normal cats and rabbits respectively.[5]

These studies indicate that the IOP effect of UF-021 is related to increased aqueous humor outflow and not to altered humor production.

c. IOP and Prostaglandins

i. Title: Endogenous prostaglandins release in radio-telemetry implanted rabbits: Rescula vs. latanoprost [Vol. 1.8; pp. 152-167]
Study Identification:
Site:
Study Dates: November 17, 1997 – February 6, 1998
Formulation and Lot No.: Rescula
Certificate Analysis: No [X]
Final Report: Nov. 10, 1999
GLP and QA Statements Signed: No [X]
Objective: "To investigate the effect of nonsteroidal anti-inflammatory pre-treatment [systemic and topical] given before the instillation of ... 0.12% UI or 0.005% latanoprost eye-dops on the intraocular pressure in radio-telemetry implanted rabbits"

Study Design – Diclofenac or saline was administered 1 hour [IM] or 30 and 15 minutes [topical] prior to instillation of either saline, Rescula [0.12%; 30 µl] or latanoprost [0.005%] BID into 1 eye of radio-telemetry implanted female New Zealand white rabbits [4-6 kg; N =5.] IOP baseline recordings were obtained for at least 2 days prior to treatment. IOP recordings were obtained for 24 hours following treatment. Each rabbit served as its own control for determination of ΔIOP. Comparison of $AUC_{\Delta IOP \text{ vs. time [mm Hg•hours]}}$ for treated eyes was compared to saline control AUC. [Note: Data were presented graphically with the exception of AUC]. Tabular data presentation for selected timepoints (e.g. hourly or q2-3 hours) would have facilitated comparison to the saline controls and baseline values.]

ii. Title: The effect of indomethacin pretreatment on the performance of 0.12% unoprostone isopropyl [Rescula] and 0.005% latanoprost [Xalatan] in normotensive dogs [Vol. 1.8; pp. 168-177]
Study Identification: Not provided

[4] Intraocular Pressure and Aqueous Humor Dynamics; Chapter V: Basic and Clinical Science Course 2000; Section 10 – Glaucoma; American Academy of Ophthalmology; 1999; pp. 14-24.
[5] Gum, G.G., Gelatt, K.N., and Ofri, R Chapter 3: Physiology of the Eye in *Veterinary Ophthalmology* 3rd Ed. [K.N. Gelatt, editor]. Lippincott, Williams, & Wilkins, New York. 1999. p.169.

Site: [redacted]

Study Dates: Not provided
Formulation and Lot No.: Rescula [redacted]
Certificate Analysis: No [X]
Final Report: June 22, 1999
GLP and QA Statements Signed: No [X]
Objective: "To investigate the effect of.... Rescula on..[IOP] in normal dogs pre-treated with indomethacin."

Study Design – The study was a 2-way crossover design with a 1-week washout period. Beagle dogs [N=4-5/group] received 2 drops in each eye of 1% indomethacin 30 and 15 minutes prior to instillation of test article. Rescula or latanoprost [0.005%] was administered to one eye and artificial tears was administered to the contralateral eye. Baseline IOP data were collected by tonometry. IOP was measured 30 minutes following treatment then q1 hour X 12 hours.

iii. Title: **Affinity profile of unoprostone for prostaglandin receptors [Vol. 1.8; pp. 178-184]**
Study Identification: Not provided
Site: [redacted]
Study Dates: Not provided
Formulation and Lot No.: Not provided
Certificate Analysis: No [X]
Final Report: July 26, 1999
GLP and QA Statements Signed: No [X]
Objective: "To determine whether unoprostone or its metabolite M_1 has affinity for any prostaglandin receptor."

Study Design – [1] [redacted] assay – Radiolabeled $PGF_{2\alpha}$, unoprostone, or its metabolite ± excess unlabeled $PGF_{2\alpha}$ was incubated with bovine corpus luteal membranes [expresses most of the PG receptors]. Competition studies were also conducted with agonists that bind at the following PG receptor subtypes: EP_1, EP_2, EP_3, IP, TP and DP Membrane bound radioactivity retained by the filter was counted. [2] Signal transduction methods – [i] Intracellular Ca^{2+} mobilization – Fura 2-AM loaded cultured human ciliary muscle cells were incubated with unoprostone or M_1 [10-1000 nM]. Fluprostenol, a $PGF_{2\alpha}$ receptor agonist, was the control. Intracellular Ca^{2+} was visualized using an excitation wavelength of 380 nm and 510 nm. [ii] Intracellular cAMP – Fresh iris-ciliary body tissue of albino rabbits was stimulated with varying concentrations of unoprostone, M_1, PGE_2, $PGF_{2\alpha}$, or latanoprost. Cells were lysed and the amount of cAMP in the supernatant was measured using the protein binding method.

Results - There was a diurnal fluctuation in IOP in normal rabbits, with higher values noted at nighttime. The decrease in IOP following 0.12% UF-021 instillation, based on $AUC_{\Delta IOP\ vs.\ time}$ [mm Hg•hours], was greater at night [-38 mm Hg•hrs] than during the day [-3.1 mm Hg•hrs]. When latanoprost was administered during the day there was an increase in AUC [+13.6 mm Hg•hrs]. Latanaprost instillation resulted in an IOP decrease comparable to UF-021 at night [-35.4 mm Hg•hrs]. Pretreatment with diclofenac did not inhibit UF-021 IOP lowering activity and appeared to increase the effect at night [AUC = -53.4 mm Hg•hrs]. Pretreatment with diclofenac did not

block the increase in IOP latanoprost during the day [AUC = +23.8 mm Hg•hrs] but inhibited the nighttime lowering activity [AUC = -15.7 mm Hg•hrs].

Data from the study in which dogs were pretreated with indomethacin should be interpreted cautiously for the following reasons: [1] there was considerable variability in the data; and [2] the contralateral eye may not be an appropriate control [e.g. untreated animals would be the preferred control]. According to the Sponsor, pretreatment with indomethacin significantly diminished both the IOP and miotic effects of Rescula. However, pretreatment with indomethacin did not modulate the IOP and miotic effects of latanoprost.

According to the Sponsor, these studies suggest that endogenous prostaglandin production in rabbits does not play a role in the IOP effect of UF-021 as it does with latanoprost, but the reverse is true in the dog.

The Sponsor states that the *in vitro* studies suggested that neither UF-021 nor M1 had affinity for the PG receptor subtypes. Data for the parent compound only was provided. However, the moiety of interest is M1. Competition assays with membrane bound FP receptor were not conducted, which is a principal receptor for $PGF_{2\alpha}$. The rank order of increase in cAMP was PGE_2 3X> M1 2X>unoprostone=latanoprost 2X>$PGF_{2\alpha}$.

C. Effects Related to Possible Adverse Reactions

i. Title: **Assessment in isolated and perfused retinal pig arteries of the vasoactive properties of unoprostone isopropyl and its metabolite M1 in comparison with latanoprost and its metabolite latanoprost acid [Vol. 1.8; pp. 184-195]**
Study Identification: Not provided
Site:
Study Dates: Not provided
Formulation and Lot No.: Not provided
Certificate Analysis: No [X]
Final Report: Feb. 12, 1999
GLP and QA Statements Signed: No [X]
Objective: "To assess the vasoactive properties of unoprostone isopropyl and its metabolite M1 [unoprostone free acid] in comparison with latanoprost and its metabolite latanoprost acid in isolated and perfused pig retinal arteries." [Graphic presentation of data.]

ii. Title: **Summary of the effect of Rescula/M1 on the effect of endothelin on contractility of isolated bovine trabecular meshwork and ciliary muscle strips [Vol. 1.8; pp. 196-201]**
Study Identification: Not provided
Site:
Study Dates: Not provided
Formulation and Lot No.: Not provided
Certificate Analysis: No [X]
Final Report: Nov. 23, 1999
GLP and QA Statements Signed: No [X]
Objective: "To assess the effect of Rescula/M1 on baseline contractility and endothelin-induced contraction of isolated strips of bovine trabecular meshwork and ciliary muscle." [Graphic presentation of data]

iii. Title: Effects of UF-021 ophthalmic solution on blood flow in rabbit ocular tissue [Vol. 1.8; pp. 202-205]
Study Identification: Not provided
Site:
Study Dates: Not provided
Formulation and Lot No.:
Certificate Analysis: No [X]
Final Report: Not provided
GLP and QA Statements Signed: No [X]
Objective: "To study the effects of UF-021 ophthalmic solution on choroidal tissue blood flow." [Graphic presentation of data. Contralateral eye used as control. A saline control group would have been more appropriate.]

iv. Title: Comparison of the effect of UF-021 ophthalmic solution, a sympathomimetic agent, and a parasympathomimetic agent on pupil diameter in rabbits [Vol. 1.8, pp. 206-212]
Study Identification:
Site:
Study Dates: September 24-27, 1991
Formulation and Lot No.:
Certificate Analysis: No [X]
Final Report: Date not provided
GLP and QA Statements Signed: No [X]
Objective: To compare "the effect on pupil diameter of UF-021 ophthalmic solution 0.12% with that of existing glaucoma treatment agents epinephrine ophthalmic solution 2% and pilocarpine ophthalmic solution 4%."

v. Title: Effect of UF-021 ophthalmic solution on an experimental conjunctivitis model in rats: Histamine-induced conjunctivitis; Allergic conjunctivitis; Carageenan-induced conjunctival edema [Vol. 1.8, pp. 213-222]
Study Identification:
Site:
Study Dates: January 10 – March 30, 1990
Formulation and Lot No.:
Certificate Analysis: No [X]
Final Report: Date not provided
GLP and QA Statements Signed: No [X]
Objective: To assess the effects of UF-021 on experimental models of conjunctivitis in the rat.

vi. Title: Effect of UF-021 ophthalmic solution on the course of repair of avulsion wounds of the corneal epithelium in rabbits [Vol. 1.8, pp. 223-230]
Study Identification:
Site:
Study Dates: January 8-26, 1990

Formulation and Lot No.:

Certificate Analysis: No [X]
Final Report: Date not provided
GLP and QA Statements Signed: No [X]
Objective: To assess "the effect of UF-021 ophthalmic solution and timolol ophthalmic solution on healing of corneal wounds in rabbits"

vii. Title: Ocular blood flow of ocular normotensive monkeys: Effects of 1-month topical treatment of 0.15% unoprostone isopropyl versus 0.005% latanoprost [Vol. 1.8, pp. 231-244]
Study Identification:
Site:
Study Dates: January 12 – March 24, 1998
Formulation and Lot No.:
Certificate Analysis: No [X]
Final Report: Sept. 8, 1999
GLP and QA Statements Signed: No [X]
Objective: "To investigate the effects of 0.15% unoprostone isopropyl ... compared with 0.005% latanoprost on the ocular blood flow after repeated topical administrations in ocular normotensive monkeys; optic nerve head flow and choroidal blood flow were measured by using laser Doppler flowmetry and choroidal perometry". [Baseline and contralateral eye served as controls.]

viii. Title: Ocular blood flow of ocular normotensive monkeys: Effects of 24-month topical treatment of 0.15% unoprostone isopropyl [Vol. 1.8, pp. 245-254]
Study Identification:
Site:
Study Dates: April 6, 1997 – April 8, 1998
Formulation and Lot No.: Not provided
Certificate Analysis: No [X]
Final Report: April 27, 1998
GLP and QA Statements Signed: No [X]
Objective: "To investigate the effects of 0.12% UIOS on the optic nerve head blood flow and on the choroidal blood flow in the foveal area using laser Doppler flowmeter, after 24-month topical administrations in ocular normotensive monkeys". [Saline controls were included]

ix. Title: Blood flow changes after systemic vasoconstrictor administration in cynomolgus monkeys: Effects of unoprostone isopropyl [UIOS] [Vol. 1.8, pp. 255-266]
Study Identification:
Site:
Study Dates: April 6, 1998 – January 21, 1999
Formulation and Lot No.: Not provided
Certificate Analysis: No [X]
Final Report: August 4, 1999
GLP and QA Statements Signed: No [X]

Objective: "To determine the effects of a single topical instillation of UIOS on baseline and ET-1-induced changes in optic nerve head and choroidal blood flow in monkeys". [Saline control group]

Study Design and Results – Under the *in vitro* conditions tested, unoprostone free acid [M1] inhibited endothelin-induced contraction of isolated bovine trabecular meshwork and ciliary muscle [low endothelin concentrations] and isolated pig retinal arteries. Rank order for potency of tested compounds in endothelin-treated pig retinal arteries was [i] intraluminal application– unoprostone isopropyl = unoprostone free acid > latanoprost acid= latanoprost; [ii] extraluminal application – unoprostone free acid = latanoprost acid > latanoprost = unoprostone.

There was a mild increase in choroidal tissue blood flow [10%] in rabbits [single dose] in the UF-021 treated eye compared to the contralateral saline treated eye and no change in ocular blood flow [optic nerve head, choroidal tissue] in monkeys treated BID for up to 24 months. Similar results were observed with latanoprost after administration to monkeys for 1 month. UF-021 abolished the ET-1 induced decrease in choroidal blood flow in the treated eye and tended to reduce the effect in the untreated contralateral eye in the monkey. [**Note:** A physiological saline control group, rather than the contralateral eye, would have been a more appropriate control.]

According to the Sponsor, the effects on the retinal arteries are in contrast to "the known vasoconstrictive actions of certain prostaglandins such as $PGF_{2\alpha}$ on large and small ophthalmic vessels". However, latanoprost, a $PGF_{2\alpha}$ analogue, also demonstrated activity in this *in vitro* assay system, especially when applied extraluminally.

No effect on pupil diameter was observed in rabbits. The Sponsor suggests that miosis was considered a species-specific response since it was not observed in other species including primates. Miosis was observed in both dogs and cats.

UF-021 instillation did not aggravate inflammation in rat models of conjunctivitis and did not inhibit repair of corneal avulsion wounds in rabbits.

D. Comparison with Other Drugs Having Similar Therapeutic Effects

i. Title: <u>Comparison of effect of UF-021 ophthalmic solution, prostaglandin E_2, and prostaglandin $F_{2\alpha}$ on intraocular pressure and local ocular findings in rabbits [Vol. 1.8, pp. 271-280]</u>
Study Identification:
Site:
Study Dates: September 15-18, 1991
Formulation and Lot No.:
Certificate Analysis: No [X]
Final Report: Date not provided
GLP and QA Statements Signed: No [X]
Objective: To compare IOP effects and local ocular effects of 0.05% UF-021, PGE_2, and $PGF_{2\alpha}$ in rabbits. [Saline control group was included.]

ii. Title: <u>Comparison of IOP-reducing action of UF-021 ophthalmic solution and existing glaucoma treatment agents in rabbits [Vol. 1.8, pp. 281-288]</u>
Study Identification:
Site:
Study Dates: September 22-24, 1987

Formulation and Lot No.:

Certificate Analysis: No [X]
Final Report: Date not provided
GLP and QA Statements Signed: No [X]
Objective: To compare IOP effects of 0.05% UF-021 to glaucoma treatments [0.5% timolol, 1% befunol, 2% epinephrine, and 4% pilocarpine] in rabbits. [Baseline values were used as control.]

iii. Title: **Comparative study of intraocular pressure lowering effects of UF-021 ophthalmic solution and carbonic anhydrase inhibitor in rabbits [Vol. 1.8, p. 289-297]**
Study Identification:
Site:
Study Dates: May 7 – August 29, 1991
Formulation and Lot No.:

Certificate Analysis: No [X]
Final Report: Date not provided
GLP and QA Statements Signed: No [X]
Objective: To compare IOP effects of ocular administration of 0.12% UF-021 to iv administration [5, 15, and 30 mg/kg] of acetozolamide in rabbits.

iv. Title: **Effects of UF-021 metabolites, UF-021 related substances, and decomposed products [degraded UF-021] on intraocular pressure in rabbits [Vol. 1.8, p. 298-303]**
Study Identification:
Site:
Study Dates: October 22-24, 1991
Formulation and Lot No.:

Certificate Analysis: No [X]
Final Report: Date not provided
GLP and QA Statements Signed: No [X]
Objective: To compare IOP effects of 0.12% UF-021 to metabolites [M1 and M2], a synthesis precursor [UF-021 Analogue A], a synthesis by-product [the trans-isomer of UF-021], 2 decomposition products, and a degradation product in rabbits.

v. Title: **The effect of 0.12% unoprostone isopropyl [Rescula] on intraocular pressure in normotensive dogs – A comparison with 0.005% latanoprost [Xalatan] [Vol. 1.8, p. 304-309]**
Study Identification: Not provided
Site:

Study Dates: Not provided
Formulation and Lot No.: Not provided
Certificate Analysis: No [X]
Final Report: Dec. 20, 1998
GLP and QA Statements Signed: No [X]

Objective: "To evaluate the effect of 0.005% latanoprost [Xalatan] and 0.12% unoprostone isopropyl [Rescula] on intraocular pressure [IOP] in normal dogs." [Graphic data only.]

Results - The table below outlines the results from these studies

Species	Test Article	Control	ΔIOP_{max}
Rabbit	UF-021 – 0.05%* PGE_2 – 0.05%* $PGF_{2\alpha}$ - 0.05%*	Saline Control Group [Baseline Values]	UF-021 - ↓8.5 [7.1] mmHg PGE_2 - ↑13.2 [12.7] mmHg up to 1 hr, ↓ 7.5 [6.7] mmHg $PGF_{2\alpha}$ ↑5.5 [5.5] mmHg up to 1 hr, ↓ 3.8 [2.2] mmHg
	UF-021 – 0.05%** Timolol – 0.5% Befunol –1% Pilocarpine – 4% Epinephrine – 2%	Baseline Values	UF-021 – ↓ 7.5 mmHg Timolol – ↓ 7.5 mmHg Befunol – ↓ 4.2 mmHg Pilocarpine – ↓ 2.8 mmHg Epinephrine – ↓ 6.5 mmHg
	UF-021 – 0.12%*** Acetazolamide – 5, 15, 30 mg/kg iv	Saline Control Group [Baseline Values]	UF-021 – ↓ 5.8 [7.1] mmHg Acetazolamide - ↓ of app. 4.5 [6] mmHg at ≥ 15 mg/kg
	UF-021**** Metabolites M1 & M2 Decomposition/Degradation Products	VH Placebo Group [Baseline Values]	UF-021 - ↓ 6.5 [9.7] mmHg M1 - ↓ 2.8 [4.9] mmHg M2 - ↓ 0.4 [2.0] mmHg Degraded UF-021 - ↓ 6.4 [8.1] mmHg
Dog	UF-021 – 0.12%***** Xalatan – 0.005%	Mean 12-hr IOP Baseline [Contralateral Eye]	Mean ↓ of app. 5 mmHg for both test articles

*No ocular irritation was observed with UF-021, conjunctival and iris hyperemia were noted with PGE_2 and $PGF_{2\alpha}$ for up to 6 hours, conjunctival hyperemia was marked in some animals administered $PGF_{2\alpha}$
**Onset of action [in hours] was timolol<UF-021<epinephrine.
***IOP effect was more sustained with UF-021.
****All concentrations were 0.12%.
*****Significant miosis seen with both drugs.

There was a comparable decrease in IOP with UF-021, timolol, epinephrine, and latanoprost under these test conditions, although time to onset of effect was slightly less for Rescula compared to some of these compounds. The decrease in IOP tended to be slightly greater with Rescula than with befunol, acetozolamide, or pilocarpine. The Sponsor states that UF-021 "was considered equipotent with timolol in these studies". The study was not designed to assess potency. M1 did not demonstrate activity in this study because it is a free acid and does not cross the cornea.

E. Interactions with Other Drugs

i. Title: **Intraocular pressure reducing action by concomitant use of UF-021 ophthalmic solution and current antiglaucoma drugs [Vol. 1.8, pp. 310-321]**
Study Identification:
Site:
Study Dates: June 7-28, 1998
Formulation and Lot No.:
Certificate Analysis: No [X]

Final Report: Date not provided
GLP and QA Statements Signed: No [X]
Objective: "To compare the effect of single-drug administration of the current antiglaucoma drugs to concomitant administration [epinephrine, timolol, pilocarpine] of the drugs and UF-021".

ii. Title: **Effect of concurrent administration of Rescula eyedrops and other antiglaucoma agents after repeated topical instillation on albino rabbit corneas [Vol. 1.8, pp. 322-368]**
Study Identification:
Site:
Study Dates: November 4, 1994 – February 3, 1995
Formulation and Lot No.:

Certificate Analysis: No [X]
Final Report: Feb. 3, 1995
GLP and QA Statements Signed: No [X]
Objective: "To study the effect of concurrent administration of Rescula eyedrops and other antiglaucoma agents after repeated topical instillation on corneas."

iii. Title: **IOP lowering effect of 0.15% unoprostone isopropyl and 0.005% latanoprost in combination in ocular normotensive radio-telemetry implanted rabbits [Vol. 1.9, pp. 1-14]**
Study Identification:
Site:
Study Dates: September 14-21, 1998
Formulation and Lot No.:
Certificate Analysis: No [X]
Final Report: Dec. 10, 1999
GLP and QA Statements Signed: No [X]
Objective: "To compare the kinetic profiles of the IOP recorded after topical administration of 10 µl 0.15% UI or 10 µl 0.005% latanoprost eye-drops or combination of 5 µl of each product in these radio-telemetry implanted rabbits."

iii. Title: **IOP lowering effect of 0.15% unoprostone isopropyl and 2% dorzolamide in combination in ocular normotensive radio-telemetry implanted rabbits [Vol. 1.9, pp. 15-29]**
Study Identification:
Site:
Study Dates: August 13, 1997 – October 12, 1998
Formulation and Lot No.:
Certificate Analysis: No [X]
Final Report: Dec. 10, 1999
GLP and QA Statements Signed: No [X]
Objective: "To compare the kinetic profiles of the IOP recorded after topical administration of 20 µl 0.15% UI or 20 µl 2% dorzolamide, a carbonic anhydrase inhibitor, or combination of 10 µl each product in these radio-telemetry implanted rabbits."

iv. Title: IOP lowering effect of 0.15% unoprostone isopropyl and 0.2% brimonidine in combination in ocular normotensive radio-telemetry implanted rabbits [Vol. 1.9, pp. 30-44]

Study Identification:

Site:

Study Dates: June 8, 1998 – February 18, 1999

Formulation and Lot No.:

Certificate Analysis: No [X]

Final Report: Dec. 10, 1999

GLP and QA Statements Signed: No [X]

Objective: "To investigate the ocular hypotensive effects of topical 0.15% UI instilled in combination with 0.2% brimonidine, a selective alpha-2 adrenoreceptor agonist, radio-telemetry implanted rabbits."

[Note: The UI and saline control animals were the same as in Study 005TEL-98.]

Results - The table below outlines the results from these studies

Species	Test Article	Control	Results
Rabbit	Timolol 0.25% Epinephrine 1% Pilocarpine 4% Administered alone or with UF-021 at 0.06%	Baseline Values	ΔIOP_{max} for combination compared to single drug administration Timolol - ↓ 2.6 mm Epinephrine - ↓ 1.8 mmHg Pilocarpine - ↓ 4 mmHg Iris and conjunctival changes was observed for up to 6 hours with timolol + UF-021 but not for single drugs or other combinations
	0.12% UF-021 alone or + 3% pilocarpine, 2% carteolol, and/or 0.04% dipivefrin X 7 days	Contra lateral eye	Based on fluorescein staining and histopathology, there were no treatment-related changes
	UF-021 0.15%, latanoprost 0.05%, or a combination	Baseline Diurnal Values	Based on AUC of ΔIOP vs. time, concomitant administration of latanoprost did not alter IOP effects of UF-021 at night [app. -30 mmHg], concomitant administration resulted in a modulation of the latanoprost ↑ in daytime IOP [+8.1 vs. +20.7], there was only a slight ↓ [≤2 mmHg] in IOP with UF-021 administered during the day
	UF-021 0.15%, dorzolamide 2%, or a combination	Baseline Diurnal Values	Based on AUC of ΔIOP vs. time, 2% dorzolamide IOP effect was greater than for UF-021 [-10.5 vs. –3.1, respectively], ΔIOP with concomitant daytime administration was comparable to dorzolamide alone [-8.5], no difference was observed at night for UF-021, 2% dorzolamide, or combination [-43.3, -40.6, -54.6, respectively]
	UF-021 0.15%, brimonidine 0.2%, or a combination	Baseline Diurnal Values	Based on AUC of ΔIOP vs. time, 0.2% brimonidine IOP effect was greater than for UF-021 [-7.5 vs. –3.1, respectively], ΔIOP with concomitant daytime administration was comparable to brimonidine alone [-8.4], no difference was observed at night for UF-021 or combination [-43.3, -46.3, respectively]

UF-021 coadministration did not inhibit the IOP effect of timolol, epinephrine, or pilocarpine. No corneal changes were observed with the concomitant administration of several antiglaucoma drugs although iris and conjunctival changes for up to 6 hours were observed with timolol + UF-021.

Coadministration of UF-021 with latanoprost, brimonidine, and dorzolamide generally increased the duration of the IOP reducing effect following night administration. In general, the daytime IOP effects of combinations were comparable to the effects for brimonidine and dorzolamide alone, but decreased the IOP daytime increase observed with latanoprost alone [Note: The data were only presented graphically.]

F. Studies Comparing Formulations

i. Title: Comparison of the effects of Rescula® eye-drops and UF-021/MS-016 on intraocular pressure and cardiovascular parameters after a single topical administration in ocular normotensive cynomolgus monkeys [Vol. 1.9, pp. 136-157]
Study Identification:
Site:
Study Dates: Not provided
Formulation and Lot No.:
Certificate Analysis: No [X]
Final Report: July 15, 1996
GLP and QA Statements Signed: No [X]
Objective: "To compare the effect of Rescula® eye-drops vs. [other UF-021 formulations] on intraocular pressure... and cardiovascular parameters after a single topical administration in ocular normotensive cynomolgus monkeys." Ocular tolerance was also evaluated.

The previous Pharmacology/Toxicology Reviewer, Dr. Andrea Weir, reviewed this study for A summary of the results of this study is provided below.

1. **Methods:** A group of male Cynomolgus monkeys received 50 µL of Rescula® and MS-016 eye drops into one eye; the contralateral eye received 50 µL of unpreserved saline solution. One group of five monkeys was used in the study, using a two-way cross-over study design with a one week wash-out period between each treatment. The animals were ancsthetized during the study.

Results - The results of this study indicate that MS-016 and Rescula® exerted comparable IOP-lowering effects in male Cynomolgus monkeys [N=5] administered a single 50 µL instillation. Following a single instillation of Rescula® eye drops, 3/5 monkeys exhibited ocular discharge and discomfort (repeated blinking and rubbing of eyes), which resolved within 24 hours. MS-016 eye drops did not elicit ocular irritation.

There were no treatment-related cardiovascular effects. There was approximately a 20% increase in MAP and HR in both treatment groups that the Sponsor attributed to anesthesia. Due to study design, a treatment-related effect can not be totally ruled out.

ii. Title: Comparison of the effects of UF-021/MS-016 eye-drops on intraocular pressure during an OD vs. BID topical administration in ocular normotensive cynomolgus monkeys [Vol. 1.9, pp. 181-198]
Study Identification:
Site:
Study Dates: Not provided

Formulation and Lot No.: [redacted]
Certificate Analysis: Yes [X]
Final Report: Dec. 18, 1996
GLP and QA Statements Signed: No [X]
Objective: To compare the IOP effects of an OD vs. BID treatment with 0.12% UF-021/MS-016 eye drop formulation for 4.5 days in ocular normotensive cynomolgus monkeys."

Study Design – UF-021/MS-016 at 50 µl was administered to one eye either OD or BID [q 6 hrs] in anesthetized [ketamine] male cynomolgus monkeys [N=5] for 4.5 days. IOP was measured [following BID treatment] and an ophthalmic exam with a focal light source was conducted BID.

Results - There was no difference in OD and BID dosing regimen with respect to IOP effects. ΔIOP for OD and BID treatment ranged from -1.2 ± 0.4 to –2.6 ± 1.5 mmHG and -1.4 ± 1.9 to -2.2 ± 1.5 mmHg, respectively, compared to baseline values. There was a contralateral IOP effect following OD but not BID treatment. There was no evidence of ocular irritation described.

G. Summary of Pharmacology – These studies need to be interpreted with the caveat that, in general, [1] they were conducted in ocular normotensive animals and [2] the majority of these studies were conducted with formulations other than that intended for clinical use. The drug substance concentration was often different from that in the clinical formulation. Based on comparative studies, both pharmacology and pharmacokinetic studies, it is not anticipated that the formulation differences with respect to excipients would significantly impact interpretation of the results.

In these studies, the rank order of sensitivity to the IOP reducing effects of UF-021 [Rescula; [redacted] was cats > rabbits > monkeys. [Maximum ΔIOP compared to placebo control (rabbit, cat) or baseline [monkey] at 0.1-0.12% concentration of drug substance was -5.7, -4.9, and -2.0 mm Hg in the cat, rabbit, and monkey, respectively.] The Sponsor proposes that the low response in monkeys is a function of species differences in the aqueous humor outflow pathways. This is consistent with the literature which indicates that uveoscleral outflow can account for 30-65% of aqueous humor outflow in nonhuman primates but only 4-14%, 3%, and 13% in humans, cats, and rabbits, respectively.[6] However, it should be noted that a similar weak response was also observed in the monkey studies with 0.5% timolol [e.g. ΔIOP_{max} of –2.5 mmHg compared to baseline values]. The Sponsor has not clearly demonstrated that uveoscleral outflow is not significantly altered by ocular instillation of UF-021, especially in the glaucomatous eye.

The decrease in IOP was dose and time-dependent. Maximum IOP reduction was usually observed within 3 hours post instillation and generally persisted for approximately 4-6 hours. UF-021 also demonstrated efficacy in a rabbit model of ocular hypertension [e.g. water loading].

The data suggest that the IOP effects of UF-021 appear to be mediated through an increase in aqueous humor outflow but not a decrease in aqueous humor flow rate [e.g. production]. [Note: The potential effects of UF-021 on aqueous humor flow rate were assessed at a concentration of 0.06%.] The Sponsor states that the data suggest that outflow is facilitated through the trabecular

[6] Gum, G.G., Gelatt, K.N., and Ofri, R Chapter 3: Physiology of the Eye in *Veterinary Ophthalmology* 3rd Ed. [K.N. Gelatt, editor]. Lippincott, Williams, & Wilkins, New York. 1999. p.169.

meshwork and not the uveoscleral outflow since the IOP effects of UF-021 were unaffected by concomitant administration of pilocarpine in rabbits and cats. Miotics are associated with a decrease in uveoscleral outflow.[7] However, pilocarpine alone in cats did not alter IOP. In addition, it is not known whether this system is sensitive enough to detect changes in uveoscleral outflow in these species in which uveoscleral outflow accounts for approximately 3% and 15% of total outflow in normal cats and rabbits, respectively.[8]

In general, UF-021 administration did not appear to alter choroidal blood flow in rabbits [single administration] or in monkeys [up to 24 months treatment]. However, in both *in vitro* [pig retinal arteries, bovine trabecular meshwork and ciliary muscle] and *in vivo* [rabbit, monkey] models, UF-021 and/or the active metabolite, M1, "abolished" ET-1 effects. According to the Sponsor, the effects on the retinal arteries are in contrast to "the known vasoconstrictive actions of certain prostaglandins such as $PGF_{2\alpha}$ on large and small ophthalmic vessels". However, latanoprost, a $PGF_{2\alpha}$ analogue, also demonstrated activity in the *in vitro* pig retinal artery assay system, especially when applied extraluminally.

The role of endogenous PG production is unclear and appeared to differ in the rabbit and dog. The reason for this difference is not readily apparent. [Note: There was some concern with respect to the conduct and data presentation in the dog study.] Despite the fact that UF-021 is a $PGF_{2\alpha}$ analogue, neither UF-021 nor its metabolite [M1] appeared to have any affinity for any PG receptor subtype, although the data were not provided for M1 binding. There was an increase in cAMP observed with incubation of UF-021, M1, or latanoprost with rabbit iris ciliary body tissue. The mechanism is not known.

Under the conditions tested and concentrations used, comparable IOP effects were observed with UF-021 and timolol in rabbits and UF-021 and latanoprost in dogs. UF-021 did not appear to inhibit the IOP effects when administered concomitantly with timolol, epinephrine, dorzolamide, brimonidine, or pilocarpine. Tolerance did not develop to UF-021 in rabbits following 50 consecutive days of treatment BID nor was there cross-tolerance with timolol.

Local effects [e.g. hyperemia of the iris and conjunctiva] [1] were observed in rabbits and cats at ≥0.12 and 0.24% of UF-021, respectively; [2] were transient lasting ≤8 hours; and [3] were inconsistently reported in the monkey at ≥0.12% UF-021. UF-021 did not aggravate inflammation in rat models of conjunctivitis nor did it inhibit corneal avulsion wound repair in rabbits.

Miosis was observed in both cats and dogs but not in rabbits or monkeys.

Data suggested a contralateral effect on IOP in the monkey but not in either the rabbit or the cat. Also in the monkey, UF-021 instillation reduced ET-1 induced decrease in choroidal blood flow in the contralateral untreated eye.

---

[7] Chapter V: Intraocular Pressure and Aqueous Humor Dynamics

[8] Gum, G.G., Gelatt, K.N., and Ofri, R Chapter 3: Physiology of the Eye in *Veterinary Ophthalmology* 3rd Ed. [K.N. Gelatt, editor]. Lippincott, Williams, & Wilkins, New York. 1999. p.169.

II. Safety Pharmacology:

A. General Pharmacology – The Sponsor conducted 3 studies to evaluate the general pharmacology of UF-021.

a. *In Vivo/In Vitro* Studies

i. Title: General pharmacology of UF-021 [Vol. 1.9; pp. 198-222]
Study Identification: Not provided
Site: [redacted]
Study Dates: July – October 1987
Formulation and Lot No.: [redacted]
Certificate Analysis: No [X]
Final Report: Date not provided
GLP and QA Statements Signed: No [X]
Objective: To assess the general pharmacology of UF-021 and compare it to $PGF_{2\alpha}$.

ii. Title: General pharmacology study of UF-021 [Vol. 1.9; pp. 198-222]
Study Identification: [redacted]
Site: [redacted]
Study Dates [In Life]: October 17 – November 30, 1990
Formulation and Lot No. [redacted]
Certificate Analysis: No [X]
Final Report: December 5, 1991
GLP and QA Statements Signed: No [X]
Objective: To assess the general pharmacology of UF-021.

iii. Title: General pharmacology study of UF-021 [Vol. 1.10; pp. 1-119]
Study Identification: Not provided
Site: [redacted]
Study Dates [In Life]: June 11- December 18, 1991
Formulation and Lot No.: [redacted]
Certificate Analysis: No [X]
Final Report: March 5, 1992
GLP and QA Statements Signed: No [X]
Objective: To assess the general pharmacology of UF-021 and its metabolite, M1.

Study Design and Results [Summary of 3 studies combined]

I. **General Condition/Behavior** –0.1, 1 mg/kg IV, Crj:CD-1 mice, N=6; No effects were observed
   i. [redacted]

II. **Central Nervous System** –0.1-10 mg/kg PO, male mice, N=2-10; No effects were observed
   i. Spontaneous motor activity
   ii. Anesthetic effect - thiopental-induced sleep, hexobarbital hypnosis
   iii. Anticonvulsive effect - pentetrazol-induced sleep, electroshock

iv. Convulsive effect – pentylenetetrazol-induced convulsions
v. Analgesic effect - acetic acid-induced writhing

III. Autonomic Nervous System and Smooth Muscle – effects, when observed, were weaker than those observed with $PGF_{2\alpha}$

i. Rat or guinea pig isolated ileum [max. 5×10^{-5} M and 1×10^{-5} gm/ml] – 20% of ACH-induced contraction in rats with UF-021; no effect in guinea pig ileum for UF-021 or M1
ii. 5HT, ACH, histamine, and barium-induced guinea pig ileum contraction [max. 1×10^{-5} gm/ml] – app. 30% and 50-80% inhibited by UF-021 at 1×10^{-6} and 1×10^{-5} gm/ml, respectively, except barium-induced contraction; no effect with M1
iii. Guinea pig isolated trachea [max. 5×10^{-5} M] – app. 15-20% of barium Cl or histamine induced contraction for UF-021; no effect with M1
iv. Isoproterenol-induced relaxation of guinea pig isolated trachea [max. 1×10^{-5} gm/ml] – no effect with UF-021 or M1
v. Rat isolated estrous uterus [max. 1×10^{-4} M] – 97% contraction rate of oxytocin with UF-021 which was stronger than that observed with $PGF_{2\alpha}$, 0% at 3×10^{-5} M in 1st study; app. 15-30% ↑ in contractile tension and 3X ↑ frequency of contraction in the nonpregnant uterus at 1×10^{-6} gm/ml for UF-021 and 1×10^{-5} gm/ml for M1, respectively, a 65%↓ contractile tension and/or 0.4X frequency rate in nonpregnant and/or pregnant uteri at 1×10^{-5} gm/ml UF-021 but not M1 in the 2nd study
vi. Rat nonpregnant uterus *in situ* [max. 1 mg/kg] – no effect on uterine motility
vii. Dog isolated blood vessel [max. 1×10^{-4} M] – 32% contraction with UF-021
viii. Guinea pig isolated thoracic aorta ± adrenaline-induced contraction [max. 1×10^{-5} gm/ml] – no effect with M1 or UF-021 alone; 21% ↑ in induced contraction with M1
ix. Rabbit isolated auricular vessels [max. 5×10^{-5} M] – no effect on perfusion pressure with UF-021
x. Guinea pig corneal reflex [0.5% maximum drug substance] – no effect

IV. Cardiovascular and Respiratory System and Temperature – 0.01-1 mg/kg iv, male anesthetized/unanesthetized Wistar rats; 0.01-10 µg/rat heart, N=2-6; generally no effect; anesthetized dogs, 1 mg/kg, maximum changes indicated below

i. Blood pressure – transient ↑ of 11 mmHg [15%] for ≤5 min [anesth.] or no change [unanesth.] in rats and 10% ↓ in dogs @30-45 min.
ii. Heart rate –rats, dogs – No effect
iii. ECG –dogs – No effect
iv. Femoral artery mean blood flow –dogs – considerable variability in all groups, no clear effect
v. Temperature – rats – No effect
vi. Coronary perfusion in isolated heart – rats – No effect
vii. Contractile force in isolated heart –rats – No effect
viii. Heart rate in isolated heart – rats – No effect
ix. ACH-induced hypotension – rats – No effect
x. Adrenaline-induced hypertension – rats – No effect
xi. Respiratory rate – dogs –transient ↑ of 79% for ≤30 min.

V. **GI System** – 0.1, 1, and/or 5 mg/kg IV and PO, male Wistar rats, N ≤6; mice, N=5; in general no effect; where effects were observed, they were weaker than those observed with $PGF_{2\alpha}$

i. Diarrheogenic/enteropooling effect -↓ of approximately 15% and ↑ of 20% in intestinal contents after PO or IV administration in rats or no effect, - ↓ of approximately 23% in mice
ii. Intestinal motility – No effect in mice
iii. Gastric emptying – No effect
iv. Gastric secretion – No effect

VI. **Platelet Aggregation Inhibition** – humans, rabbits; no effect with either UF-021 and M1[rabbits only]

i. ADP-induced aggregation – No effect

VII. **Water and Electrolyte Metabolism** – 0.1, 1 mg/kg IV, Wistar rats, N=6; In general, no effect was observed

i. ↓ 10-30% in urine Na, K, Cl

VIII. **Bleeding Time** – 1 mg/kg, male Crj:CD-1 mice, N=10

i. No effect observed with UF-021 and M1

b. *In Vitro Studies*

i. **Title:** [redacted] compound Cba-1 for Ciba Vision

Study Identification: [redacted]
Site: [redacted]
Study Dates: May 29 – July 15, 1999
Formulation and Lot No.: Not provided
Certificate Analysis: No [X]
Final Report: July 20, 1999
GLP and QA Statements Signed: No [X]
Objective: To assess the enzyme and tissue receptor binding activity of the UF-021 metabolite, M1.

Study Design and Results– Radioligand binding assays were conducted with a test article identified as Cba-1 [Alternative code – M1]. Results are presented as IC_{50} [nonlinear, least squares regression analysis], K_I, or Hill coefficients. No significant interaction [≥50%] was observed [1] at muscarinic, tachykinin NK_1, and thromboxane A_2 receptors, and K channels up to 30 μM; [2] at α_1 and α_2, β_1 and β_2 adrenergic receptors, NE transporter, $endothelin_{A \text{ and } B}$, glucocorticoid, leukotriene B_4 and D_4, melatonin, muscarinic $M_{2, 3, 4, \text{ and } 5}$ and nonselective, neuropeptide Y_2, and tachykinin NK_3 receptors, Ca channel Type L, K channels K_A, K_{ATP}, K_v, and $5K_{CA}$ up to 10 μM; and did not interact with ATPase H^+/K^+ [30 μM] and Na^+/K^+ [100 μM], and protein kinase A, nonselective [100 μM].

B. Summary of Safety Pharmacology –General pharmacology [general behavior, CNS, autonomic nervous system, smooth muscle, cardiovascular and respiratory system, temperature, GI system, water and electrolyte metabolism, platelet aggregation and bleeding time, and binding characteristics] was evaluated both *in vitro* and *in vivo* in rats, mice, dogs, and guinea pigs. Route of administration was either IV or PO except in the corneal reflex evaluation where UF-021 was

instilled into the conjunctival sac. Doses ranged from 0.1-10 mg/kg and maximum concentrations used were 5 X 10^{-5} and 1 X 10^{-4} M. UF-021 and/or M1 demonstrated activity in *in vitro* systems as follows: [1] mild contraction [≤50% of reference article effect] of isolated rat ileum, dog blood vessels, and guinea pig trachea; [2] potentiation [app. 20%] of adrenaline-induced guinea pig thoracic aorta contraction; [3] partial inhibition [≤80%] of serotonin, acetylcholine, and histamine-induced contraction of guinea pig ileum; and [4] concentration dependent increase or decrease of contractile tension and/or frequency of contraction in rat pregnant and nonpregnant uterus. [Note: No effect on uterine motility was observed *in vivo* in nonpregnant rats at a maximum dose of 1 mg/kg.] UF-021 and/or M1 demonstrated activity in *in vivo* systems as follows: [1] transient increase in blood pressure [app. 15%] in anesthetized but not unanesthetized dogs or rats; [2] transient increase in respiratory rate [app. 80%] in dogs; [3] increase or decrease in enteropooling effect depending on route of administration; and [4] a decrease [app. 10-30%] in urine Na, K, and Cl. In general, the observed effects of UF-021 were weaker than those observed with $PGF_{2\alpha}$. No other treatment-related effects were identified under the conditions tested.

III. Pharmacokinetics/Toxicokinetics:

A. Ocular Biodistribution/Bioavailability Studies

a. *In Vitro* Studies

i. Title: *In vitro* corneal permeation of unoprostone isopropyl [UF-021] and its metabolization in the isolated pig eye [Vol 1.50, pp.21-41] – This study is described below under Metabolism [B.a.i]

ii. Title: Comparison of the *in vitro* corneal permeation of MS-016 and Rescula® eye drop formulations [Vol. 1.50, pp. 1-20]
Study Identification:
Site:
Study Dates: Not provided
Formulation and Lot No.: Rescula
Certificate Analysis: Yes [X]
Final Report: July 23, 1996
GLP and QA Statements Signed: No [X]
Objective: "To compare the *in vitro* corneal permeation of two eye formulations containing...isopropyl unoprostone"

Dr. Andrea Weir previously reviewed this study ***The review of this study is provided below with additional comments by the current Reviewer in bold italics.***

Methods: The methods used in these studies are provided in the table below.

Methods Used in Pharmacokinetics Studies

Study	Methods
Corneal Permeation	

Results -The *in vitro* corneal permeation study revealed that the two formulations had essentially identical corneal permeation characteristics. The total amount of drug substance that crossed the cornea was low. ***[Data suggest that corneal permeation of UF-021 is <1% of the applied dose.]*** The parent compound was completely hydrolyzed by corneal esterases to the acid form.

b. *In Vivo* Studies

i. Title: Comparison of the *in vivo* ocular penetration of unoprostone isopropyl versus unoprostone free acid [Vol. 1.50; pp. 324-333]
Study Identification:
Site:
Study Dates: Not provided
Formulation and Lot No.
Certificate Analysis: Yes [X]
Final Report: November 16, 1998
GLP and QA Statements Signed: No [X]
Objective: "To compare the ocular penetration ... of UF-021 and ... M1 eye-drops formulation after repeated instillation into the conjunctival sac of New Zealand rabbits."

Study Design – UF-021 or M1 was administered at 30 µl into the conjunctival sac of one eye of female New Zealand albino rabbits [3.5-4 kg; N = 6] q 1 hour X 3. Vehicle was administered to the contralateral eye. The amount of UF-021 and M1 permeating the cornea was measured by

Results – Neither M1 nor UF-021 was detected in aqueous humor after instillation of M1. M1, but not UF-021, was detected at all time points in the aqueous humor after instillation of UF-021. [Note: Data for UF-021 administration only were provided.]

c. Single Dose Ocular Biodistribution - The results of 4 studies are summarized together.

i. Title: Ocular penetration of UF-021, A new prostaglandin-related compound, in the rabbit eye [1992] Watanabe, C., et. al., *Acta Soc. Ophthalmol. Jpn.*, 96[3]:335-339 [Vol. 1.50, pp. 42-51]
Study Identification: Not provided
Site:
Study Dates: Not provided
Formulation and Lot No.:
Certificate Analysis: No [X]
Final Report: Date not provided
GLP and QA Statements Signed: No [X]
Objective: "To assess the ocular biodistribution of 0.12% UF-021 in pigmented and non-pigmented rabbit eyes."

Study Design – Radiolabeled UF-021 [35 µl] was instilled 1X into the conjunctival sac of one eye of either albino [N=6] or Dutch Belted [N=4] male rabbits, app. 3-mo. old. Thirty-five µl

of "base composition" was instilled into the contralateral eye. Animals were sacrificed 10, 20, and 40 minutes, 1, 2, 4, 8, and 24 hours after dosing for nonpigmented eyes and 40 minutes, 2, 4, 8, and 24 hours after dosing for pigmented eyes. Radioactivity was measured in plasma, cornea, anterior and posterior sclera, iris, ciliary body, crystalline lens, vitreous, retinochoroid, and optic nerve.

ii. Title: Distribution of UF-021 in rabbit eye tissue after single topical administration [Vol. 1.50, pp. 52-70]
Study Identification:
Site:
Study Dates: April – July 1991
Formulation and Lot No.:
Certificate Analysis: No [X]
Final Report: Date not provided
GLP and QA Statements Signed: No [X]
Objective: "To assess the ocular biodistribution of 0.12% UF-021 in pigmented and non-pigmented rabbit eyes."

Study Design - Radiolabeled UF-021 [35 µl/42 µg] was instilled 1X into the conjunctival sac of one eye of either albino [N=3] or Dutch Belted [N=3] male rabbits, app. 3-mo. old. Thirty-five µl of "base composition" was instilled into the contralateral eye. Animals were sacrificed 15 and 30 minutes, 1, 2, 4, 8, and 24 hours after dosing for nonpigmented eyes and 40 minutes, 1, 2, 6, and 24 hours after dosing for pigmented eyes. Radioactivity was measured in plasma, cornea, anterior and posterior sclera, iris, ciliary body, crystalline lens, vitreous, retinochoroid, and optic nerve.

iii. Title: Comparison of ocular bioavailability of two UF-021 eyedrop formulations, Rescula® and MS-016, after a single instillation in the pigmented rabbit [Vol. 1.50; pp. 108-236]
Study Identification:
Site:
Study Dates: July 7 – August 29, 1996
Formulation and Lot No.:
Certificate Analysis: Yes [X], p. 227 and 232
Final Report: November 4, 1997
GLP and QA Statements Signed: Yes [X]
Objective: "To compare the bioavailability of 0.12% ...UF-021 eyedrop formulations ... after a single instillation of ^{3}H-formulated eyedrop...into the conjunctival sac...of pigmented rabbits.

Dr. Andrea Weir previously reviewed this study ***The review of this study is provided below with additional comments by the current Reviewer in bold italics.***